New Drug Review:
2009 Update

John K. Jenkins, M.D.
Director, Office of New Drugs
Center for Drug Evaluation and Research

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Housekeeping

- Today's talk is an updated version of last year's talk, which was apparently well received (you invited me back!)
- Data and analyses presented are thought to be accurate, but have not undergone thorough quality control as is performed for official FDA reports
- Many staff in CDER provided data for this talk
  - A special acknowledgement to Michael Lanthier for his outstanding help in conceiving and conducting many of the analyses. His behind the scenes work makes me look good.

Topics to be covered

- What were your priorities for new drug review in 2009 and how did you do?
- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
- FDA/EMEA approval comparisons

2009 Review Priorities

- Recruitment and training of new staff
  - CDER and OND have completed a very successful 24-month recruiting effort
  - Funding to support the new staff comes from increased Congressional appropriations and increases under PDUFA IV
  - Our focus is now shifting from recruiting to training so that new staff can be fully productive, which can take 1-3 years depending on the position

Recruitment FY08

	CDER	OND
FY08 FTE Ceiling	2882	890
Onboard 10/1/07 (# under ceiling)	2236 (-646)	731 (-159)
New hires during FY08	663	209
Onboard 9/30/08 (# under ceiling	2632 (-250)	852 (-38)
Net gain FY08	396	121

Recruitment FY09

	CDER	OND
FY09 FTE Ceiling	3060	930
Onboard 10/1/08 (# under ceiling)	2632 (-428)	852 (-78)
New hires during FY0	490	142
Onboard 9/30/09 (# under ceiling	2996 (64)	924 (-6)
Net gain FY08	364	72

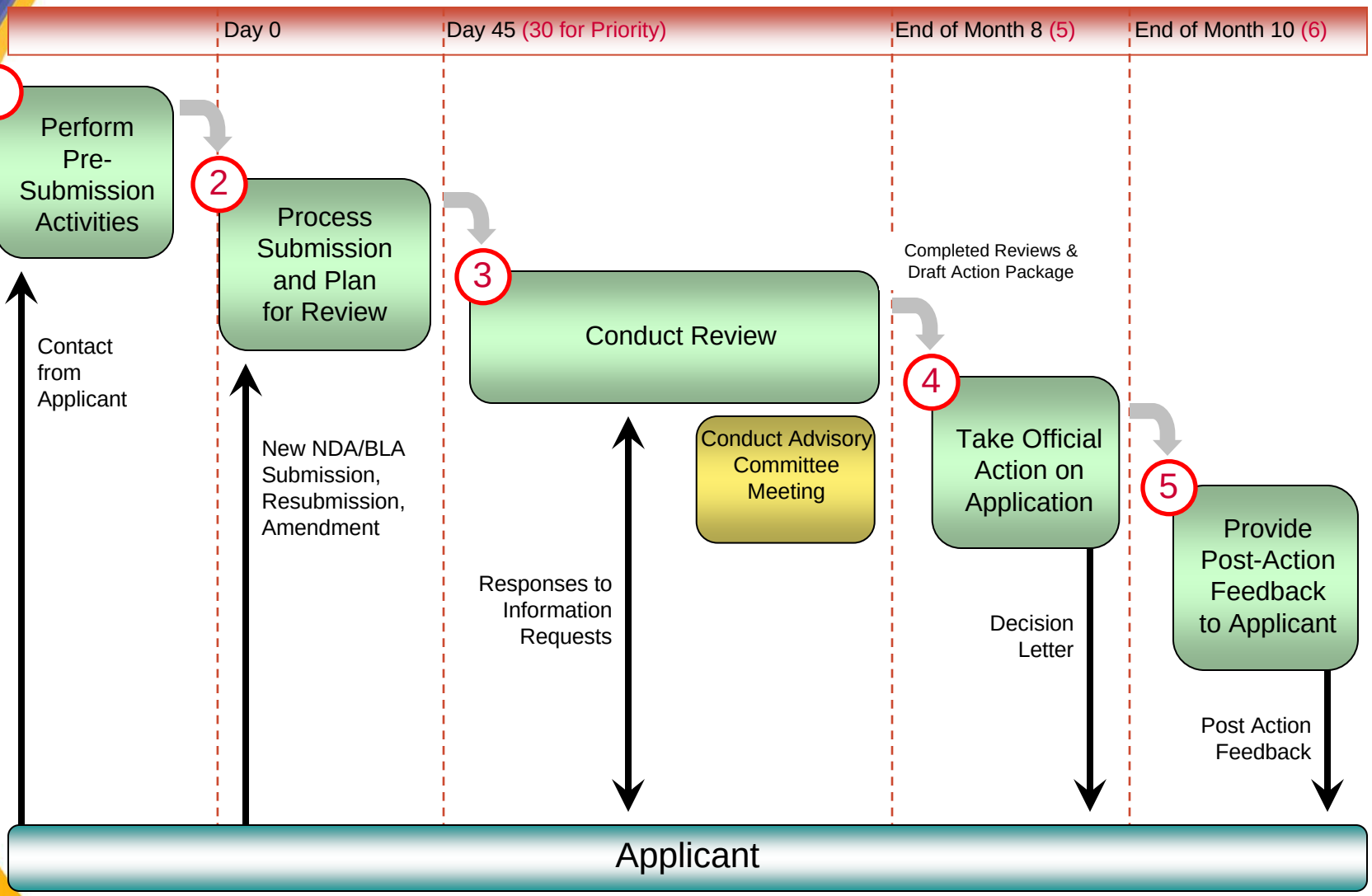
FY10 Staffing Realities

- Significant net increase in new staff in past 24 months, which is great!!
  - CDER: 760 FTEs (34% increase)
  - OND: 193 FTEs (26% increase)
- However, 38% of current CDER and OND staff have <2 years experience on the job
  - The full impact of new staff on CDER performance will not be seen for another couple of years
- CDER White Oak space is full
  - Working to address space needs for current and future new employees

2009 Review Priorities

- Implement 21st Century Review Process
  - New review process developed to embed principles of GRMP into our day-to-day review
  - New process emphasizes:
    - Expectation for complete applications at time of submission
    - Review planning and timelines for deliverables
    - Cross-disciplinary teamwork & communication
    - Work distribution throughout the review cycle
    - Involvement of signatory authority early/often
    - Protection of time for end-of-review activities
    - Greater transparency to sponsor

21st Century Review Process



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Implementation Status and Plans

- New review model was applied to all NME NDAs and original BLAs in FY09
- Extensive training of review staff in new process and teamwork skills continues
- Steering Committee continues to oversee process rollout and enhancements
  - Ongoing auditing to assess compliance
- New review model applies to all Efficacy Supplements for a new or expanded use in FY10
- Full phase-in will be complete by end of FY12 (parallels phase-in of PDUFA IV goals for notification of sponsors of review timeline

Lessons Learned & Challenges

- Change of such a complex process is very hard,!!
  - More challenging for experienced staff
- Standard procedures that everyone follows are critical, and are a work in progress
- Complete, high-quality applications at time of submission are critical!!
- Increased number of foreign manufacturing and clinical sites is straining ability of field to complete inspections in time to meet PDUFA goal dates
- Holding an Advisory Committee and meeting priority review goal is very difficult
- Incorporating development and approval of a complex REMS during the first review cycle is almost impossible
  - Must plan well in advance (e.g., EOP2 or pre-NDA/BLA meeting) for complex REMS to allow possibility for a first-cycle approval

Advisory Committees

- CDER policy is that most, but not all, NME NDAs and original BLAs will be discussed at a public AC
  - Responds to the intent of FDAAA provision
  - Improves transparency of review process
  - Provides FDA with important expert and public input
- Increased use of AC however creates a strain on FDA resources and brings challenges related to empanelling committees with appropriate experts without significant COI (financial or intellectual)

CDER ACs FY09

FY	# AC Meetings	Advisors Screened (#/ Meeting)	Advisors Cleared (% of screened)	Waivers Approved (% of cleared)
2006	26	400 (15)	362 (90%)	131 (36%)
2007	25	554 (22)	440 (78%)	80 (18%)
2008	27	489 (18)	380 (78%)	26 (7%)
2009	43	875 (20)	663 (75%)	12 (2%)

2009 Review Priorities

- Continue Implementation of Safety First Initiative
  - The goal of Safety First is to bring the same level of priority and project management to postmarketing safety issues that is applied to application review
  - Safety First also ensures that all appropriate disciplines and expertise are applied to review of postmarketing safety issues to ensure sound decisions
  - Safety First continues emphasis on early communication to the public and greater transparency to FDA decisions

Safety First Status

- Dedicated staff in OND IO and each OND division to manage safety portfolio
- Developing standardized procedures, roles, expectations
  - MaPPs finalized: Tracking Significant Safety Issues in Marketed Drugs, Establishing and Operating Safety Issues Teams in CDER
- 815 Tracked Safety Issues (TSI) have been generated for tracking/follow up since 1/07
  - Over 400 TSI are currently under active review
- 44 Safety Communications were issued in FY09 that named 88 drugs
  - Many involved class safety issues (e.g., AEDs/suicidality, ADHD drugs/sudden death, TNF blockers/cancer, transdermal patches/MRI burns)

2009 Review Priorities

- Continue Implementation of FDAAA (Title IX)
  - Landmark legislation providing FDA with expanded authorities to manage the entire life-cycle of drugs
    - Ability to require Risk Evaluation and Mitigation Strategies (REMS) to ensure safe and effective use of drugs
    - Ability to require postmarketing studies or trials to assess serious safety issues
    - Ability to order safety related labeling changes
  - Many detailed timelines and deliverables included in the legislation

Title IX Status

- Steering Committee oversight continues
- Developing standardized procedures, roles, expectations
  - Draft guidances issued: REMS, PMC/PMR
  - MaPPs issued: Developing PMC/PMR, Tracking PMC/PMR
- Working to begin decentralization of clearance process for FDAAA actions
  - Slow process due to the complexity of the legal requirements and the fact that each case seems to raise new challenges/issues
- “Deemed” REMS
  - 2 approved
  - 13 others under active review

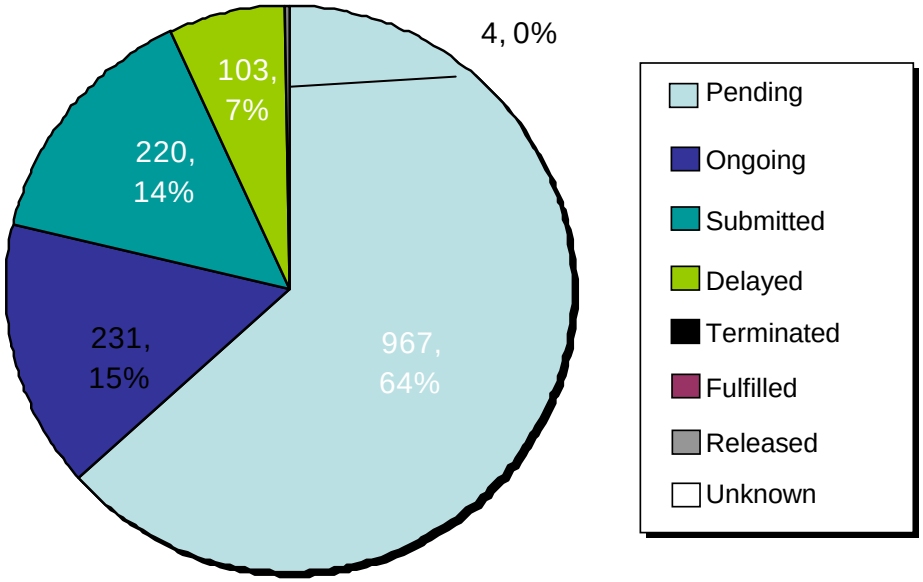
CDER FDAAA Title IX Actions

(as of 11/19/09)

Total REMS Approved	88
Medication Guide only REMS	64
REMS with a communication plan	21
REMS with ETASU	9
Total PMRs	84
Safety labeling changes (19 “class” changes, 9 individual products)	28
Safety labeling orders (ESAs, olanzapine)	2

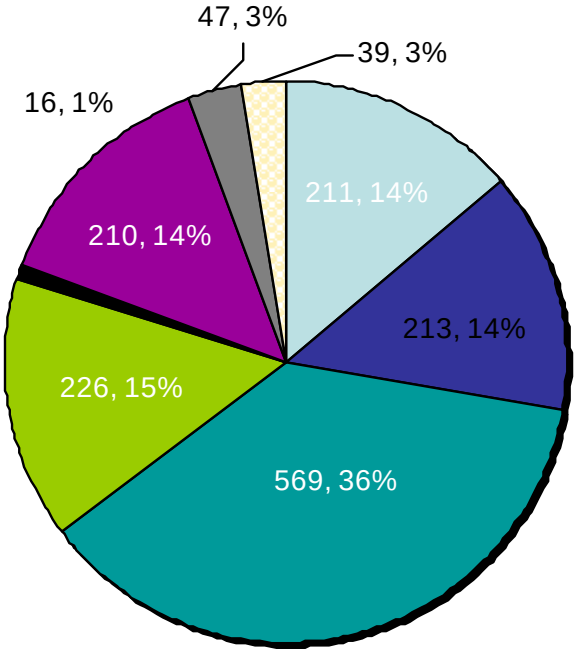
PMC/PMR Database Cleanup

Backlog PMRs/PMCs by Status Before Review*



Total = 1531

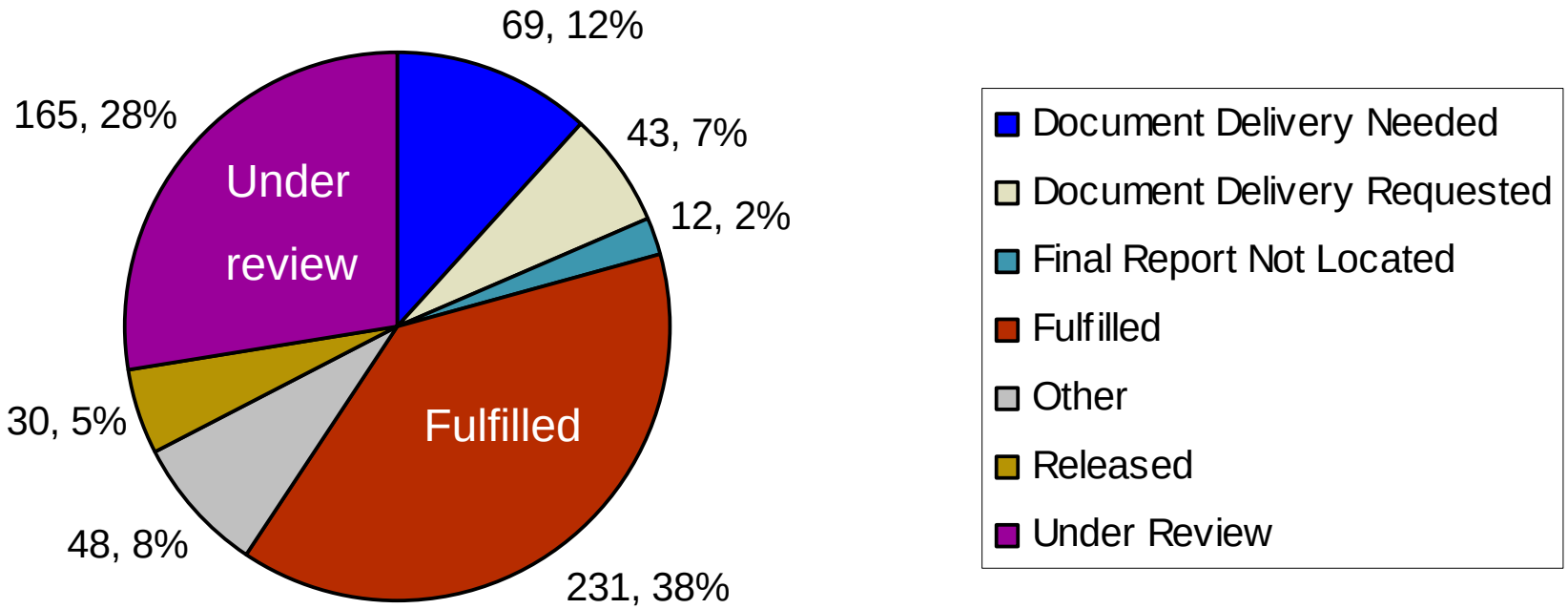
Backlog PMRs/PMCs by Status After Review



Total = 1531

Submitted Report Backlog Review

(as of November 30, 2009)



*Note: “Other” includes 38 final reports that have been reviewed, however a letter has not yet been sent

What about PDUFA Goals?

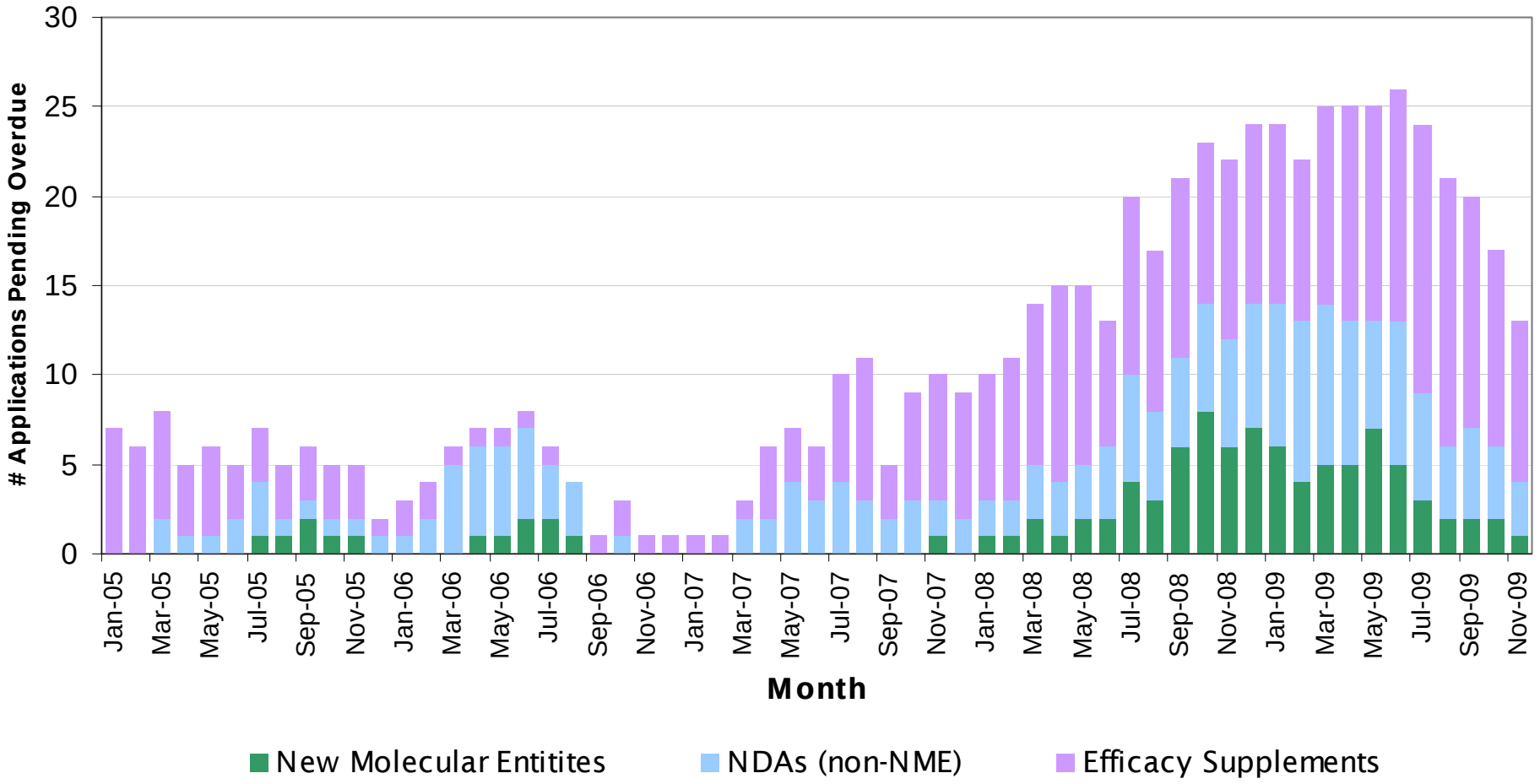
- FDA continues to take PDUFA goals very seriously
  - These are commitments that we made to Congress and the American public for how we will do our work
- In November 2007 I granted permission for OND managers to exercise greater flexibility regarding PDUFA goals due to workload/resource constraints
- In October 2009 I instructed OND managers to begin moving back to our prior posture of meeting PDUFA goals whenever possible; i.e., “permission withdrawn”

CDER FY08 Application Review

(applications submitted in FY08, status as of September 30, 2009)

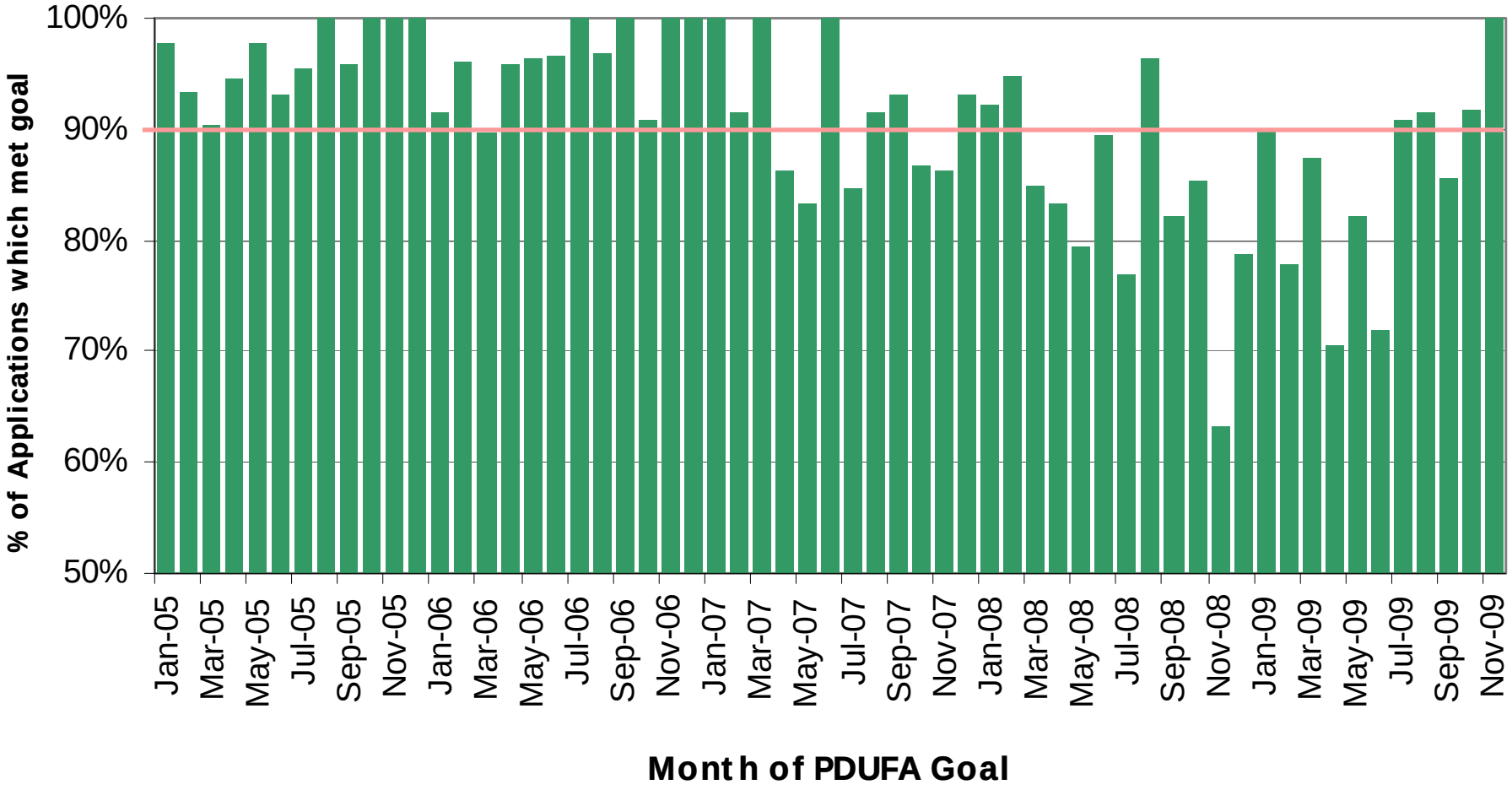
Submission Type	Number Filed*	2007 Performance Goal	Current Performance
NDAs/BLAs			
Standard	102	90% in 10 months	84%
Priority	30	90% in 6 months	63%
NMEs/New BLAs			
Standard	24	90% in 10 months	83%
Priority	13	90% in 6 months	69%
NDA / BLA Resubmissions			
Class 1	18	90% in 2 months	94%
Class 2	35	90% in 6 months	74%
NDA / BLA Efficacy Supplements (ES)			
Standard	104	90% in 10 months	85%
Priority	37	90% in 6 months	92%
NDA / BLA ES Resubmissions			
Class 1	11	90% in 2 months	73%
Class 2	30	90% in 6 months	87%
NDA / BLA Manufacturing Supplements			
Requiring Prior Approval	632	90% in 4 months	86%
CBE	1178	90% in 6 months	93%

Pending Applications with Overdue PDUFA Goals by Month



Source: CDER Data as of 11-30-2009, excluding biologic license applications (BLAs)

Performance on NDA and Efficacy Supplement PDUFA Goals by Month



Source: CDER Data as of 11-30-2009, aggregate performance for all NDAs and efficacy supplement PDUFA goals, including resubmissions. Accounts for goal date extensions where applicable. Excludes data for biologic license applications (BLAs)

What about new drug approvals?

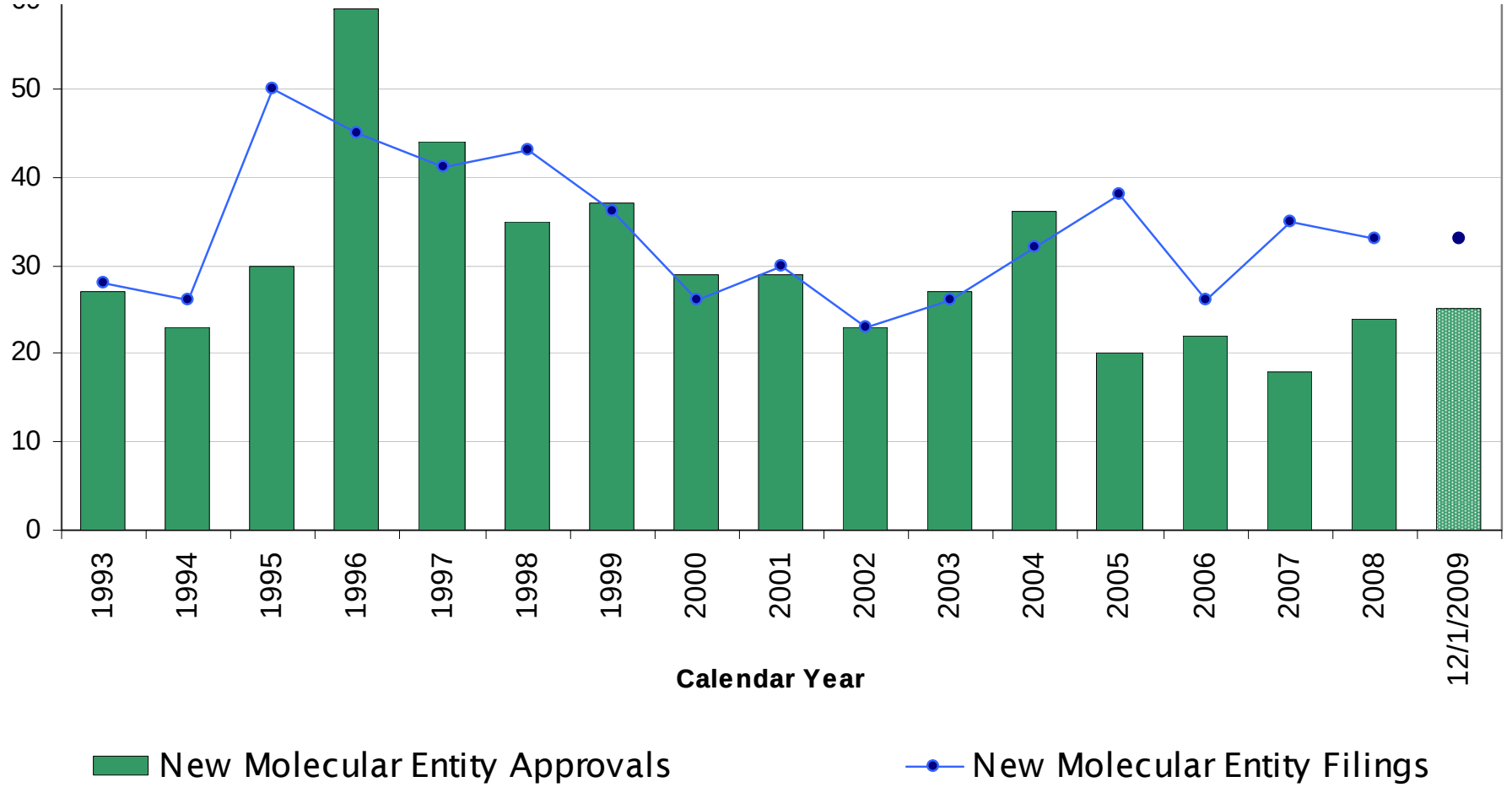
- The debate about whether FDA is too fast or too slow in approving new drugs continues to rage
  - In fact, we hear complaints from both sides of the issue at the same time!!
- In my 17 ½ years at FDA I have never received or issued an order to “speed up” or “slow down”
- We review each application on its merits and apply our best judgment with regard to the data, the science, and the regulations
- We do not have goals for numbers of approvals by year, division, etc.
  - Drugs that meet the standards for approval are approved
  - Drugs that do not meet the standards are not approved

What metric to follow for trends?

- We believe the most appropriate metrics are those based on submission cohorts; i.e., by FY
  - Unfortunately, submission cohorts take time to mature; analysts and the media are impatient for results
- Approval cohorts; i.e., by CY, provide more timely information
  - Unfortunately these analyses are analogous to averaging apples and oranges

CDER NME Filings and Approvals

Calendar Year Data (Approval Cohort)



Source: CDER Data as of 12-1-2009

CY09 NME Approvals

Trade Name	Active Ingredient	Summary Indication
Savella	milnacipran HCl	fibromyalgia
Uloric	febuxostat	hyperuricemia in gout patients
Afinitor	everolimus	renal cell carcinoma
Coartem	artemether; lumefantrine	malaria
Ulesfia	benzyl alcohol	head lice
Simponi	golimumab	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis
Dysport	abobotulinumtoxin A	cervical dystonia, glabellar lines
Fanapt	iloperidone	schizophrenia
Samsca	tolvaptan	hypervolemic and euvolemic hyponatremia

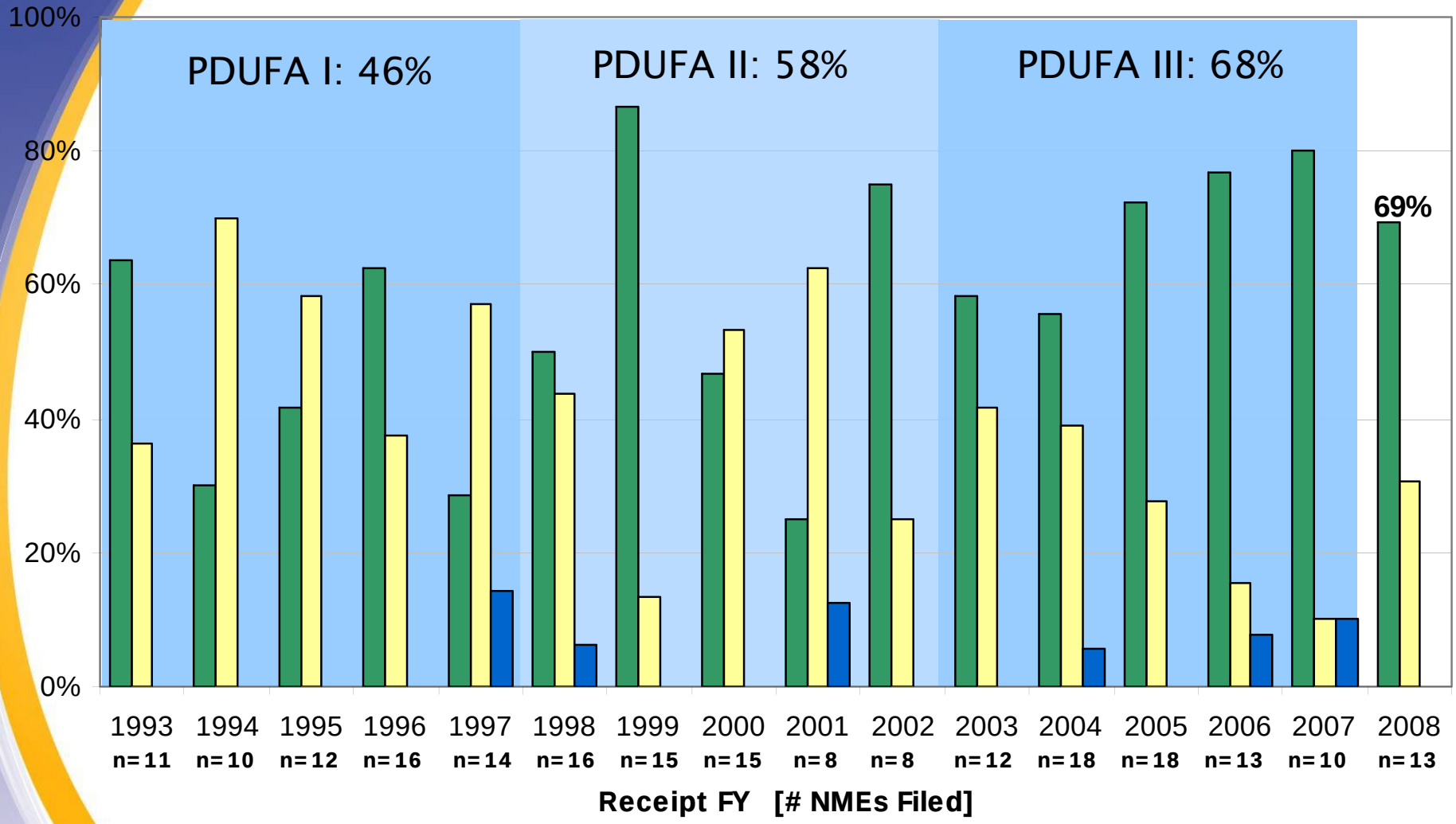
CY09 NME Approvals (cont.)

Trade Name	Active Ingredient	Summary Indication
Besivance	besifloxacin	bacterial conjunctivitis
Ilaris	canakinumab	Cryopyrin-Associated Periodic Syndromes (CAPS)
Multaq	dronedarone HCl	atrial fibrillation (AF), atrial flutter (AFL)
Effient	prasugrel	reduction of thrombotic CV events in patients with acute coronary syndrome (ACS) undergoing PCI
Onglyza	saxagliptin	type 2 diabetes
Livalo	pitavastatin	cholesterol lowering
Saphris	asenapine	schizophrenia, bipolar disorder
Sabril	vigabatrin	complex partial seizures, infantile spasms

CY09 NME Approvals (cont.)

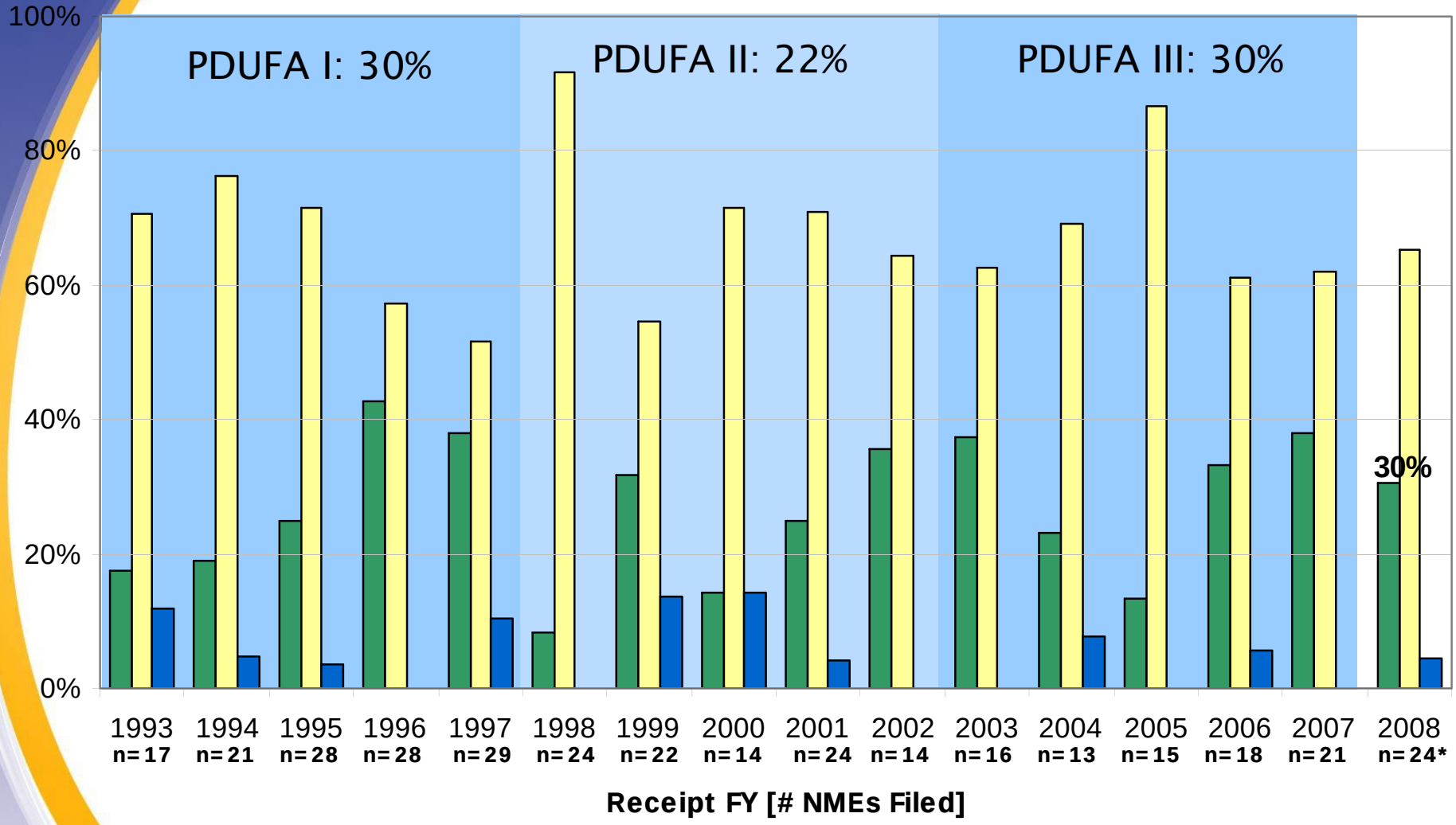
Trade Name	Active Ingredient	Summary Indication
Bepreve	bepotastine besilate	allergic conjunctivitis
Vibativ	telavancin	complicated skin and skin structure infections (cSSSI)
Folotyn	pralatrexate	peripheral T-cell lymphoma (PTCL)
Stelara	ustekinumab	moderate to severe plaque psoriasis
Votrient	pazopanib HCl	renal cell carcinoma
Arzerra	ofatumumab	chronic lymphocytic leukemia (CLL)
Istodax	romidepsin	cutaneous T-cell lymphoma (CTCL)
Kalbitor	ecallantide	hereditary angioedema

First Action Approval Rates: Priority NMEs (FY Submission Cohort)



Source: CDER Data as of 11-30-2009

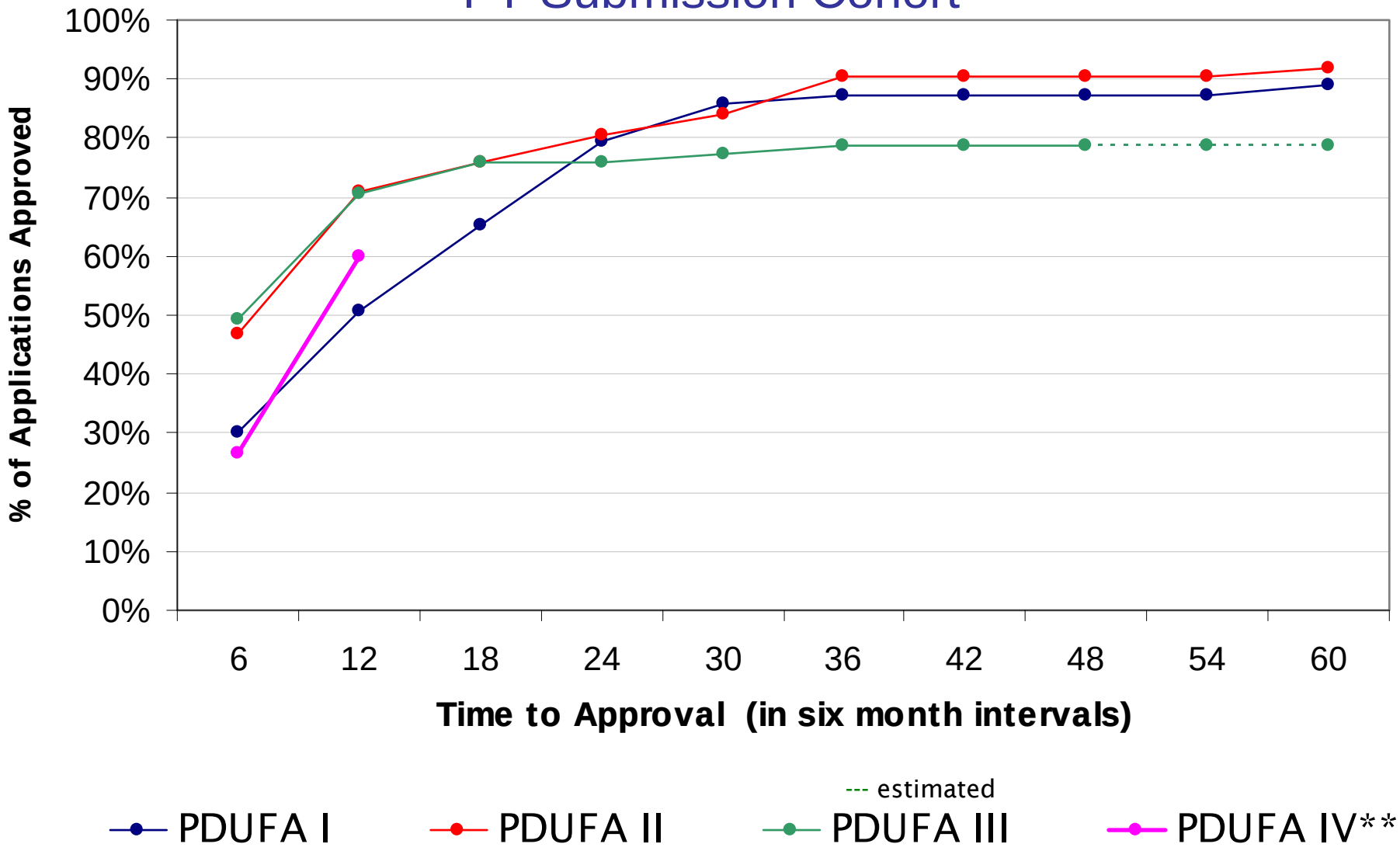
First Action Approval Rates: Standard NMEs (FY Submission Cohort)



Source: CDER Data as of 11-30-2009. * first action rates for FY 2008 based on 23 actions to date

Time to Approval – Priority NMEs

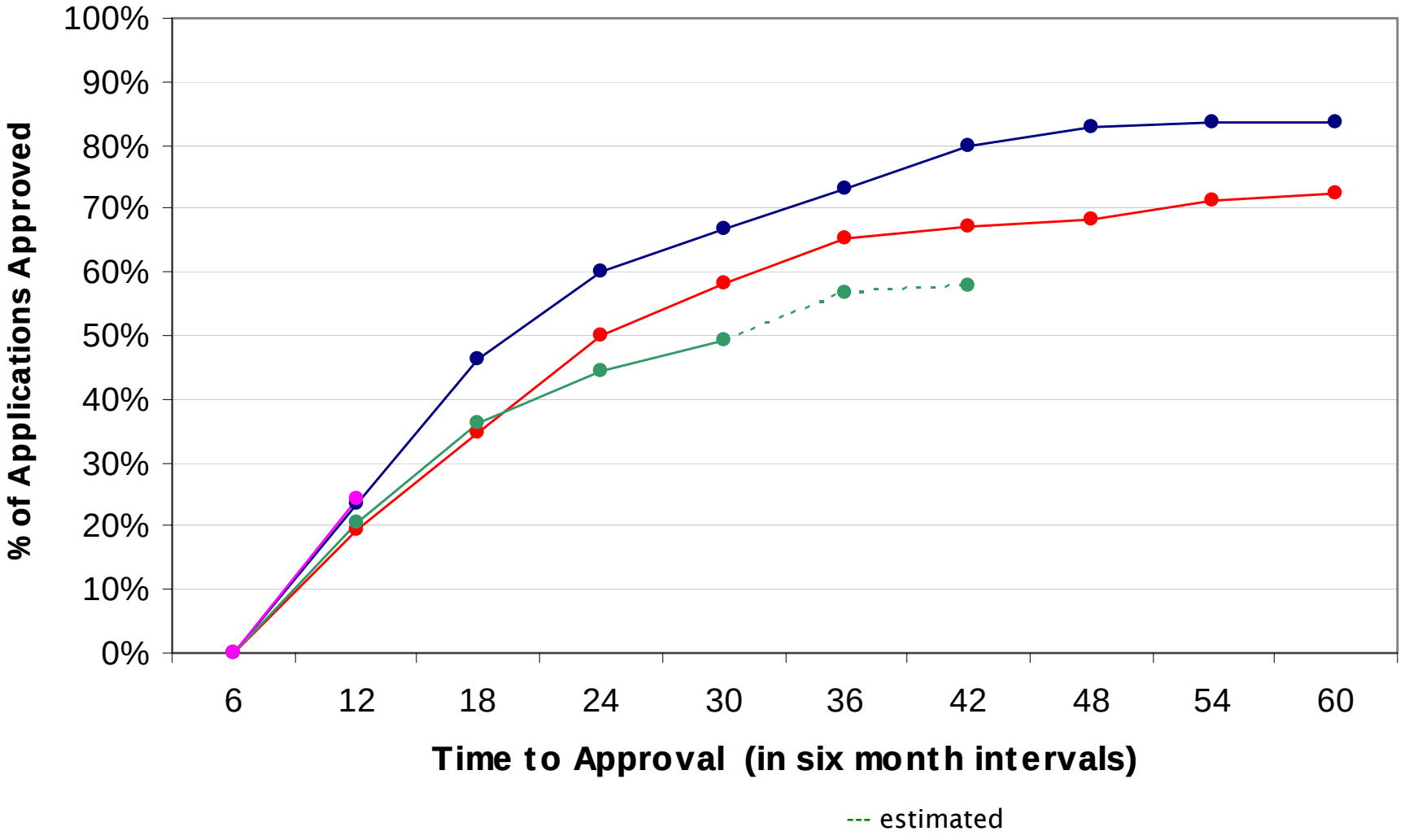
FY Submission Cohort



Source: CDER Data as of 10-31-2009. ** preliminary PDUFA IV figures based on 15 priority NME submissions received through 12/31/2008

Time to Approval – Standard NMEs

FY Submission Cohort

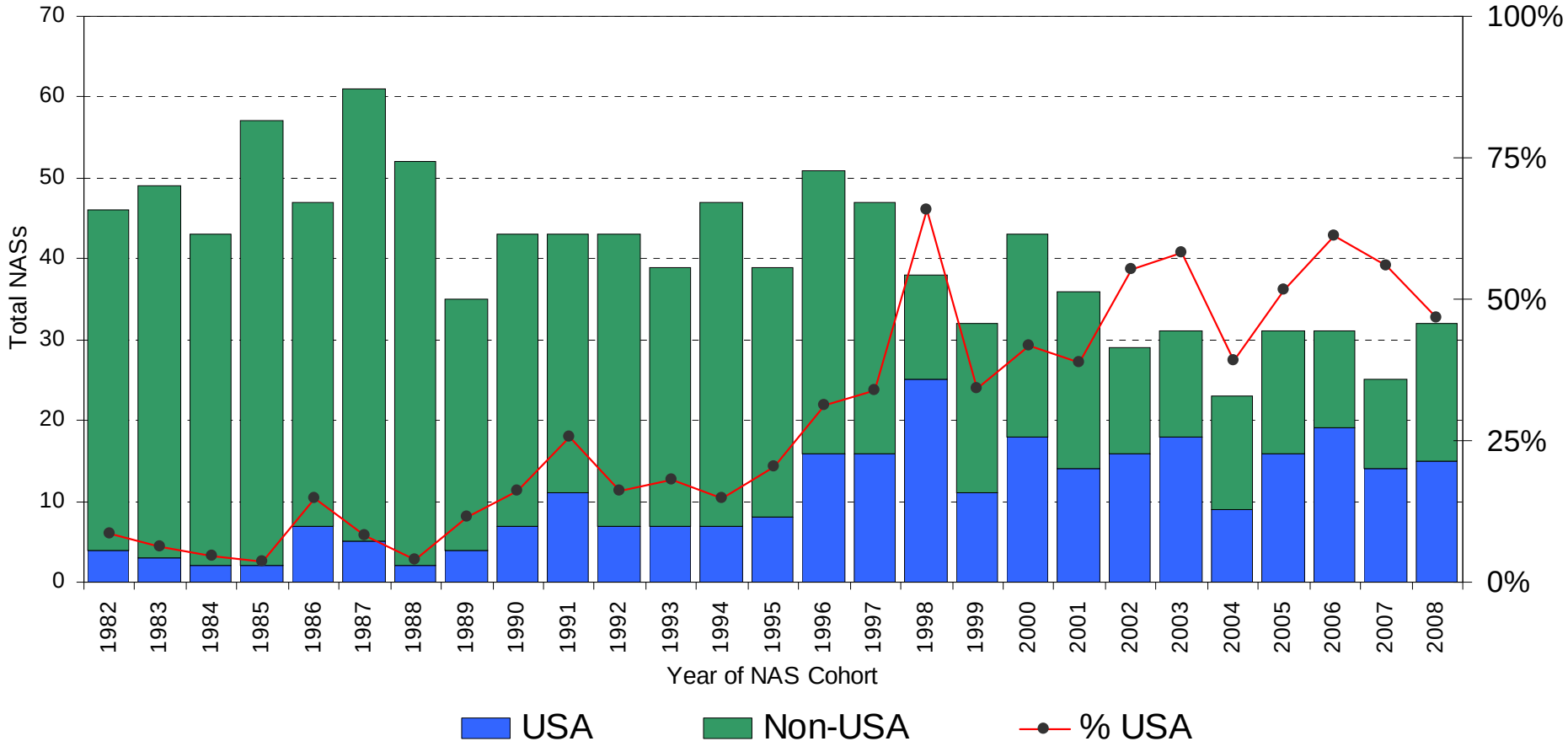


Source: CDER Data as of 10-31-2009. ** preliminary PDUFA IV figures based on 33 standard NME submissions received through 12/31/2008

But, isn't EMEA faster and less "conservative"?

- The FDA and EMEA approval systems are very different, but often work in "parallel"
  - Most NMEs are submitted to both agencies
  - Submission timing is generally within 6-12 months between the agencies
- Some sponsors and analysts have stated that FDA has become too "conservative" and that EMEA is approving drugs faster than FDA
  - While comparisons are interesting, we do not consider ourselves to be in a race with other regulatory agencies

USA Share of New Active Substances First Launched on World Market



Source: Scrip NCE Review/Scrip Yearbook/Scrip Magazine (1982 -2005), PharmaProjects R&D Annual Review (2006-2008)

Comparison of NME Outcomes: FDA and EMEA

(Jan 2006 – October 2009)

	# of NMEs Reaching First Regulatory Action[a]	Approval Outcome[b]	Non-Approval Outcome	% Approved during time frame
FDA	126	77	49	**61%**
EMEA	135	92	43	**68%**

[a] FDA figures do not include resubmissions of NDAs that were first acted on prior to 2006.

[b] Approval outcomes include approval following NDA resubmission to FDA or revised opinion following re-examination by CHMP during this timeframe.

Source: CDER data as of 10-31-09 and EMEA published information (EMEA annual reports, published lists of refusals and withdrawals, published CHMP Monthly Plenary Meeting reports). These figures only include drugs that would be considered NMEs based on CDER's definition for New Molecular Entities.

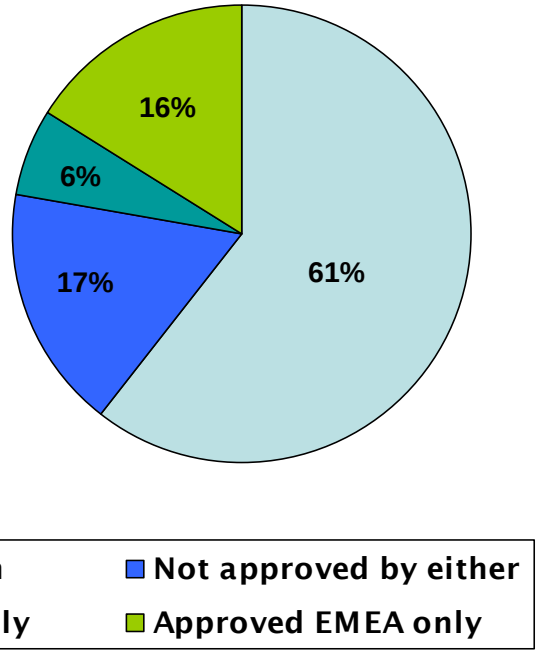
Comparison of NME Outcomes: FDA and EMEA

- Analysis includes 81 novel drugs submitted to both FDA and EMEA that meet the following criteria:
  - NMEs (including therapeutic BLAs) submitted to both FDA and EMEA for the same indication
  - Marketing application was received by FDA and EMEA within 12 months of each other
    - Actual difference <6 months in 85% of cases
  - Regulatory action has been taken by both authorities ***and*** decision by the CHMP occurred after 1/1/06 (EMEA began publishing CHMP recommendations for marketing applications on 12/20/05)
  - Outcomes in both regulatory agencies are tracked through 10/31/09.
  - Sponsor withdrawal of a marketing application was classified as a non-approval outcome

NMEs with Similar Submission Timing having Outcomes at both FDA and EMEA

(Jan 2006 – October 2009) *n = 81*

Regulatory Outcome	#
Approved by both Authorities	49
Not Approved by either Authority	14
Approved by FDA only	5
Approved by EMEA only	13

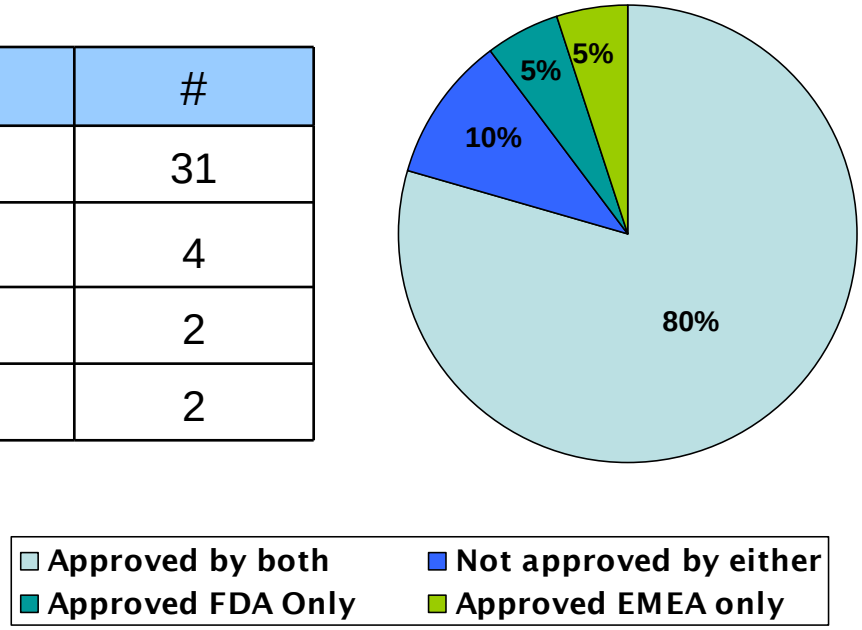


Source: FDA data and EMEA published information (EMEA annual reports, published lists of refusals and withdrawals, published CHMP Monthly Plenary Meeting reports). These figures only include drugs that would be considered NMEs based on CDER's definition for New Molecular Entities.

Priority NMEs with Similar Submission Timing having Outcomes at both FDA and EMEA

(Jan 2006 – October 2009) *n = 39*

Regulatory Outcome	#
Approved by both Authorities	31
Not Approved by either Authority	4
Approved by FDA only	2
Approved by EMEA only	2

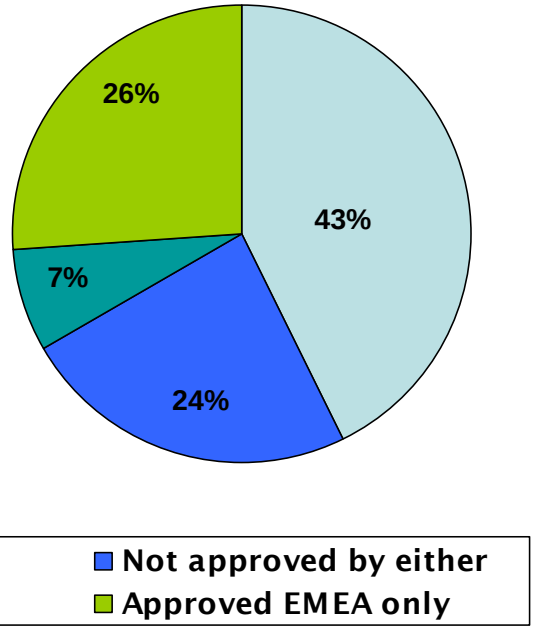


Source: FDA data and EMEA published information (EMEA annual reports, published lists of refusals and withdrawals, published CHMP Monthly Plenary Meeting reports). These figures only include drugs that would be considered NMEs based on CDER's definition for New Molecular Entities.

Standard NMEs with Similar Submission Timing having Outcomes at both FDA and EMEA

(Jan 2006 – October 2009) *n = 42*

Regulatory Outcome	#
Approved by both Authorities	18
Not Approved by either Authority	10
Approved by FDA only	3
Approved by EMEA only	11



Source: FDA data and EMEA published information (EMEA annual reports, published lists of refusals and withdrawals, published CHMP Monthly Plenary Meeting reports). These figures only include drugs that would be considered NMEs based on CDER's definition for New Molecular Entities.

Divergent NME Outcomes

Approved by EMEA, not approved (yet) by FDA

- Galvus (vildagliptin) - type 2 diabetes
- Thelin (sitaxsentan sodium) - pulmonary arterial hypertension
- Mepact (mifamurtide) – resectable non-metastatic osteosarcoma
- Acomplia (rimonabant) - obesity
- Preos (parathyroid hormone) – treatment of postmenopausal osteoporosis
- Firazyr (icatibant acetate) - hereditary angioedema
- Tredaptive (nicotinic acid/laropiprant) – cholesterol lowering
- Bridion (sugammadex) - reversal of neuromuscular blockade
- Actemra (tocilizumab) - rheumatoid arthritis
- Fablyn (lasofoxifene) - treatment of postmenopausal osteoporosis
- Xarelto (rivaroxaban) - prevention of VTE in hip or knee replacement surgery
- Yondelis (trabectedin) - relapsed ovarian cancer
- Onbrez Breezhaler (indacaterol maleate) - chronic obstructive pulmonary disease

Divergent NME Outcomes

Approved by FDA, not approved (yet) by EMEA

- Revlimid (lenalidomide) – deletion 5q myelodysplastic syndromes
- Ixempra (ixabepilone) - metastatic or locally advanced breast cancer
- Cimzia (certolizumab pegol) - Crohn's disease
- Savella (milnacipran hydrochloride) - fibromyalgia
- Vibativ (telavancin) - complicated skin and skin structure infections

Other Divergent Outcomes

• Several NMEs that reached outcomes in the EMEA after January 1, 2006 were submitted to FDA more than 12 months ahead of the EMEA marketing application and therefore do not appear in our sample of 81 drugs. Several of these had divergent outcomes as well:

Approved by FDA, not (yet) approved by EMEA

- Factive (gemifloxacin mesylate) – community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis
- Mylotarg (gemtuzumab ozogamicin) – acute myeloid leukemia
- Rozerem (ramelteon) – insomnia
- Pristiq (desvenlafaxine) – depression
- Iplex (mecasermin rinfabate) - primary growth hormone insensitivity
- Zolinza (vorinostat) - cutaneous T-cell lymphoma

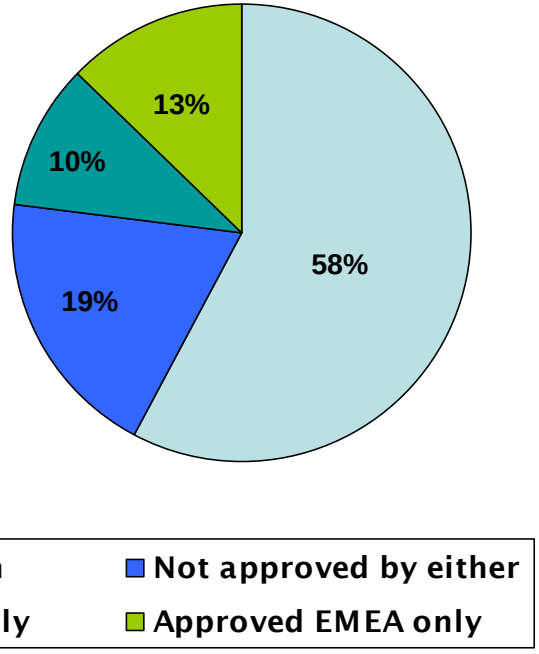
Approved by EMEA, not approved (yet) by FDA

- Conbriza (bazedoxifene) – treatment of postmenopausal osteoporosis

NME applications with EMEA actions since 1/1/06 that have also reached FDA action (without regard to timing of submissions or action dates)

n = 109

Regulatory Outcome	#
Approved by both Authorities	63
Not Approved by either Authority	21
Approved by FDA only	11
Approved by EMEA only	14



Source: FDA data and EMEA published information (EMEA annual reports, published lists of refusals and withdrawals, published CHMP Monthly Plenary Meeting reports). These figures only include drugs that would be considered NMEs based on CDER's definition for New Molecular Entities.

FDA/EMEA Comparisons

- Concordance of action for ~80% of NMEs submitted within 12 months to both agencies
- Little divergence on priority NMEs, greater divergence on standard NMEs
  - Probably not surprising given the lower public health priority of standard NMEs and the fact that many of these decisions are close judgment calls (i.e., marginal, but statistically significant efficacy and safety concerns)
- FDA and EMEA communicate and share information on many applications, but we conduct independent assessments and make decisions based on distinct laws, regulations, precedents, and societal expectations

Questions?